

### **Remarks/Arguments**

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-124 are pending in this application and are rejected on various grounds. Claim 124 has been canceled without prejudice or disclaimer. Claim 119 has been amended for clarity. The rejections to the presently pending claims are respectfully traversed.

### **Information Disclosure Statement**

Applicants submit an IDS separately enlisting references recited in the Blast report filed 3/25/2002 in order to be compliant with 37 C.F.R. § 1.98(a)(1). Consideration of this Information Disclosure Statement is respectfully requested.

### **Specification**

The disclosure was objected to by the Examiner as containing “embedded hyperlink and/or other form of browser-executable code.” The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

Accordingly, Applicants believe that all objections to the specification has been overcome.

### **Claim Rejections – 35 USC § 101 and 112, First paragraph**

Claims 119-124 are rejected under 35 U.S.C. §101 allegedly “because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.” Claims 119-124 are further rejected under 35 U.S.C. §112, first paragraph allegedly “since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention”.

As discussed below under priority, Applicants submit that they rely on the gene amplification assay for patentable utility of PRO1112 and its antibodies, which was first disclosed in U.S. Provisional Application 60/113,296, filed December 22, 1998, priority to which has been claimed in this application. Hence, the effective filing date of the present application should at least be **December 22, 1998**.

While the Examiner acknowledges, on page 5 of the instant Office Action, that the positive hit in a gene amplification assay establishes utility for the PRO1112 nucleic acid, the Examiner contends that it does not establish utility for PRO1112 polypeptides or its antibodies. The Examiner specifically noted that the data in the specification was not supported by the analysis of mRNA or polypeptide expression and quotes exemplary references like Pennica *et al.* and Konopka *et al.* to show that "it does not necessarily follow that an increase in gene copy numbers results in increased gene expression and increased polypeptide expression" and further quotes Haynes *et al.* to show that "even if gene amplification correlates with increased transcription, it does not always follow that protein levels are also amplified". For the reasons outlined below, Applicants respectfully disagree.

### **Utility Standard**

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial"

utility.” (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: “If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.”

Finally, the Utility Guidelines restate the Patent Office’s long established position that any asserted utility has to be “credible.” “Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant’s assertions.” (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

### **Arguments**

As discussed under the section on "priority", Applicants rely on the gene amplification data for patentable utility for the PRO1112 gene and the PRO1112 protein and antibodies thereof.

### **A *prima facie* case of lack of utility has not been established**

The Examiner bases the assertion that increases in gene copy number do not reliably correlate with increased gene expression or polypeptide expression, on exemplary literature reports like Pennica *et al.*, Konopka *et al.* and Haynes *et al.* and hence concludes that the PRO1112 polypeptides and their antibodies lack utility.

According to the Examiner, Pennica *et al.* teaches that “An analysis of *WISP*-1 gene amplification and expression in human colon tumors **showed a correlation between DNA amplification and over-expression**, . . . . In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient.” (Emphasis added). Firstly, Applicants draw attention to Pennica's showing that “a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene” in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica teaches nothing of the correlation between gene amplification and polypeptide over-expression in general.

Further, the Examiner cites the abstract of Konopka *et al.* to establish that “[p]rotein expression is not related to the amplification of the *abl* gene . . . .” Again, Applicants respectfully submit that the Examiner has generalized a result pertaining to merely **one** gene, the *abl* gene, to cover all genes in general. Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification. Applicants submit that the Konopka reference is not sufficient to establish such a *prima facie* showing of lack of utility based on the results with the *abl* gene alone. Thus, the combined teachings of Pennica and Konopka are not directed towards genes in general but to single genes or genes within a family and thus, their teachings have been misinterpreted in this rejection.

Finally, the Examiner cites the Haynes *et al.* reference to establish that “even if gene amplification correlates with increased transcription, it does not always follow that protein levels are also amplified.” The Examiner adds that “Haynes *et al.* studied 80 proteins... and found no strong correlation between proteins and transcript levels.” Applicants respectfully traverse and point out that, on the contrary, Haynes teaches that “**there was a general trend** but no strong

correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). For example, in Figure 1, there is a positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins studied but the correlation is "not linear" and hence, "one cannot **accurately** predict protein levels from mRNA levels." In fact, very few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. In fact, the Haynes data, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Thus, Applicants submit that the Examiner's rejection is based on a misunderstanding of the scientific data presented in Haynes *et al.*

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification: polypeptide over-expression, as observed for the *WISP-2* or the *abl* genes, is typical. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Pennica *et al.*, a correlation between DNA amplification: polypeptide over-expression was observed in the case of *WISP-1* and similarly, in Haynes *et al.*, **most genes** showed a correlation between increased mRNA : translated protein. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

**It is "more likely than not" for amplified genes to have increased mRNA and protein levels**

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, just as in Haynes, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss

of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Also enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA.

While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the art of genes that do not fit within the central dogma of molecular biology, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1112 gene, that the PRO1112 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1112 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

**Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence**

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the

practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1112 polypeptide, for example, in detecting over-expression or absence of expression of PRO1112. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Accordingly, Applicants request that the present 35 U.S.C. §101 and §112, first paragraph rejections to the pending claims be withdrawn.

#### **Claim Rejections – 35 USC § 112, second paragraph**

Claims 119-124 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner asserts that "neither the art nor provide a clear definition for, or distinction between, "binds" and "specifically binds. Therefore, the metes and bounds of the claimed invention cannot be determined".



Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled claim 124 and have amended claim 119 to recite "specifically binds". Applicants submit that the term "specific binding" or "specifically binds" has a well established meaning, and is understood by those skilled in the art to mean that the antibody binds to a particular polypeptide, and does not significantly bind to another polypeptide. Since claim terms should be given their ordinary, art-recognized meaning, the present rejection is believed to be misplaced, and should be withdrawn.

### **Priority**

The Examiner asserts that the instant specification fails to provide a disclosure meeting the requirements of 35 U.S.C. § 101 and 112, first paragraph and thus denies priority to any parent application and grants priority only to the instant filing date.

However, as discussed above, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1112 polypeptide and its antibodies, for example, in detecting over-expression or absence of expression of PRO1112.

Applicants have previously asserted priority to U.S. Provisional Application 60/113,296, filed December 22, 1998 and rely on its disclosure of the PRO1112 gene, the protein sequence and gene amplification assay data for patentable utility of PRO1112 and its antibodies. Based on the above discussions on utility, the provisional application is similarly has utility and hence, the effective filing date of the present application should at least be **December 22, 1998**.

### **Claim Rejections – 35 USC § 102(b)**

Claims 119 and 124 are rejected under 35 USC 102(b) as being anticipated by Rolls *et al.* (1999).

As discussed above, Applicants are entitled to the effective filing date of at least be **December 22, 1998**, based on their priority claim. Hence, Rolls *et al.* is not prior art. Therefore, this rejection to the pending claims must be withdrawn.

### **Claim Rejections – 35 USC § 103**

Claims 120-123 are rejected under 35 USC 103(a) as being unpatentable over Rolls *et al.* (1999) in view of U.S.P.N. 5,874,082- De Boer.

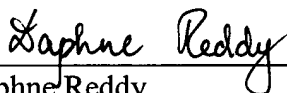
As discussed above, Applicants are entitled to the effective filing date of at least be **December 22, 1998**, based on their priority claim. Since the primary reference, *Rolls et al.* is not prior art, this rejection falls and Applicants submit that the instant claims are not obvious over *Rolls* in view of *De Boer*. Therefore, this rejection to the pending claims must be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C14). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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